IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Lyons et al.	) PATENT
Serial No.:	10/732,862	) Attorney Docket) LOR-136.0
Filed:	December 10, 2003	) (9720/88881)
For:	STABILIZED IMMUNOGENIC HBc CHIMER PARTICLES	)
Examiner:	Bo Peng	) Group Art No.) 1648

APPELLANTS' BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an Appeal from the Office Action mailed March 3, 2009, at least twice rejecting claims 1-47. A Notice of Appeal was filed on September 1, 2009 with applicable fees. A Notification of Non-Compliant Appeal Brief was mailed on June 3, 2010, due to the Appeal Brief being in the new format because the USPTO is now considering the final rule anew.

Should there be any deficiency in fees in connection with this Appeal, the Commissioner is respectfully requested to

and is hereby authorized to charge any such deficiency in fees to Deposit Account No. 23-0920.

STATEMENT OF THE REAL PARTY IN INTEREST

Celldex Therapeutics, Inc., the assignee, is the real party in interest.

STATEMENT OF RELATED APPEALS AND INTERFERENCES

There are two related appeals. One is regarding pending U.S. Application No. 11/508,655 to Lyons et al., filed August 23, 2006, and the other is regarding pending U.S. Application No. 09/930,915 to Birkett et al, filing dated August 15, 2001.

STATUS OF CLAIMS

Claims 1-47 are pending and have been at least twice rejected. The rejections of claims 1-47 are being appealed. A copy of the pending claims appears in the Claims Appendix.

STATUS OF AMENDMENTS

The amendments to claims 1, 11, 25 and 47 proposed in the Response of 1-20-09 were entered. The claims with these amendments are listed in the Claims Appendix.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention contemplates a recombinant chimer hepatitis B core (HBc) protein molecule that is engineered for enhanced stability and substantial absence of nucleic acid binding. The HBc portion of the molecule is preferably truncated at the C-terminus, having about 125 amino acid residues in comparison to the native HBc molecule sequence, which is 183 amino acids in length. The molecule is comprised of amino acid residues 4-75 and about 85-140 of the HBc amino acid sequence, with either or both cysteine 48 and cysteine 107 being substituted by another amino acid. (Page 7, paragraph [0088], lines 42-54 of published application US2004/0146524). In addition, cysteine 61 must be present. (Page 5, paragraph [0058], lines 10-11).

The molecule also contains a peptide-bonded heterologous amino acid sequence at either the N-terminus, C-terminus or between amino acids 76-85 (the HBc immunodominant loop). (Page 8, paragraph [0090}, lines 20-26).

The heterologous sequence can be one to about 245 amino acids in length, which can represent an immunogen, an anti-antigen, or a chemically-reactive linker residue for a

conjugated hapten of one to about 40 amino acids in length. (Page 8, paragraph [0091], lines 40-47).

The immunodominant loop of the molecule can exist in several forms; all of the amino acids can be present, all can be absent, some can be absent, and in any of these forms, one or more amino acids can be substituted for another. (Page 8, paragraph [0091], lines 38-49).

In addition, a contemplated molecule contains additional cysteine residues (one or more up to three total) located near either or both ends of the molecule. The location near the N-terminus corresponds to amino acids -20 to +1 relative to the amino acid sequence of HBc shown in SEQ ID NO:1. The location near the C-terminus corresponds to that within about 30 residues from the C-terminus of the chimer molecule. (Page 8, paragraph [0098], lines 56-62 and Page 9, paragraph [0098], lines 1-4).

A contemplated molecule can also have up to about 5 percent of the amino acid substituted corresponding to SEQ ID NO:1. (Page 26, par. [0233])

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1) Whether Claims 1-47 are unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

2) Whether Claims 1-47 are unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

3) Whether Claims 1-6, 8-14, 16-28, 30-42 and 46 are unpatentable under 35 U.S.C. §103 as being obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) and Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429).

4) Whether Claims 1-47 are unpatentable under 35 U.S.C. §103 as being obvious over Page et al. (WO 01/98333) and Birkett (U.S. Patent Number 6,231,864) in view of Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429).

5) Whether Claims 1-46 are unpatentable under obviousness-type double patenting, as being obvious over (1) claims 1-78 of 09/930,915; (2) claims 1-53 of 10/787,734; (3) claims 98-109 of 10/805,913; (4) claims 79-115 of 10/806,006; (5) claims 47-85 of 11/508,655; (6) claims 1-22, 25, 26 of 11/507,083.

6) Whether Claims 1-6, 8-28, and 30-46 are unpatentable under obviousness-type double patenting, as being obvious over claims 1-19 of U.S. Patent Number 6,231,864 in view of Page et al. (WO 01/98333) and Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429.

ARGUMENT

1) Claims 1-47 Claims Comply with the Written Description Requirement

In contrast to allegations asserted in the Final Office Action, Claims 1-47 do satisfy the written description requirement. The facts are that the Office Action of March 3, 2009 rejected claims 1-47 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Action alleged that the claims contained subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. (See page 2, sections 4-7 of Office Action of 3-3-09).

The Action asserted in the first sentence of section 5, that the claims encompass a large number of HBc chimers that contain a 5% substitution frequency in SEQ ID NO:1. The second sentence of section 5 of the Action asserted that such particles

have enhanced stability as compared to wild-type (wt) HBc. (See page 4, section 5 of the Office Action of 3-3-09).

Neither of these statements is properly reflective of the current claims. The claims do not simply recite HBc chimers that contain 5% substitution in the HBc sequence. Nor do the claims simply recite the limitation of the chimers having enhanced stability compared to the wt, even though this fact is true. Claims 25-46 recite that the particles demonstrate enhanced stability shown by size exclusion chromatography after storage at 37°C in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month.

Therefore, the arguments made to show that the claims do not satisfy the written description requirement are not on point at the very start.

The Action next states that 14 of the 24 tested HBc chimers in Table 13, lost their ability to form particles. (See page 4, section 5 of the Office Action of 3-3-09) Further, the Action alleges that this shows that it is uncertain if HBc chimers containing a 5% substitution frequency can form particles with enhanced stability.

These arguments also are also not on point. The current claims have a limitation of *one or both cysteine residues at positions 48 and 107 replaced by another residue*.

This limitation has not been taken into account in the Action's assertions. The current claims also have a limitation of *containing one or both of 1-3 cysteine residues at the N-terminus or C-terminus.* This limitation also has not been taken into account by the Action.

In fact, Table 13, upon which the Action relies in its arguments, does not contain any molecules reflective of the present claims. Of the 24 molecules shown, none contain **all** of the limitations recited in the claims, such as having a heterologous epitope, having C48 and/or C107 substitutions, and having 1-3 cysteines on both or either terminus.

Only four molecules (chimer nos. 1794, 1775, 1780, and 1789) of the 24 shown in Table 13 have cysteine 48 and/or 107 substitutions. Table 13 shows that chimers whose wild-type counterpart formed particles, also formed particles (chimer nos. 1775 and 1789) when the cysteines were substituted. (See Published Patent Application No. US 2004/0146524, page 65, Table 13).

The β-amyloid epitope, which failed to assemble into a stable particle in cysteine 48- and/or 107-containing form (chimer no. 1510), also failed to assemble in cysteine 48- and/or 107-substituted form (chimer no. 1794). The ASP-1 epitope cysteine 48- and/or 107-containing form (chimer no.

1546) behaved like the engineered, cysteine 48- and/or 107-substituted form (chimer no. 1775), as both formed particles. The anthrax epitope failed to assemble into a stable particle in the non-cysteine-substituted form (chimer no. 1629) and also failed to assemble in the engineered, cysteine-substituted form (chimer no. 1780). The influenza epitope in the non-cysteine-substituted form (chimer no. 1569) formed particles as did the engineered form (chimer no. 1789).

However, there was a purification problem with the influenza engineered particles as the engineered form seemed to stick to the HYPATITE™ column and recovery was therefore lower than the non-engineered form. (See [paragraph 0533]). Also, in recent work with the influenza epitope, it has been shown that, when displayed in the loop, this epitope is prone to cleavage. It is thought that monomers would cleave, regardless of loop stabilization, simply due to the nature of the epitope.

In short, Table 13 provides evidence that C48S/C107S-substituted, epitope-added chimer forms have similar capabilities in forming particles as do their non-C48S/C107S-substituted counterparts. This is confirmed by the data in Table 12, which show that C48S/C107S molecules having C-terminal cysteines without epitope inserts also successfully assembled into particles. (See paragraph [0522-0524]) Therefore, because

there is evidence in the specification that the claimed molecules, which contain both epitope inserts, C48/C107 substitutions and one or more terminal cysteines, successfully formed particles, this evidence reasonably conveys to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. It is therefore respectfully requested that this rejection be withdrawn.

It is further noted that the claimed subject matter recites a test for stability that compares particles formed without the C48S/C107S modification (wt) to particles with that modification. Thus, if the wt chimer did not form particles, there would be nothing against which to compare once the C48S/C107S modification was in place. This basis for rejection should be withdrawn.

2) Claims 1-47 Comply with the Enablement Requirement

In contrast to allegations asserted in the Final Office Action, claims 1-47 satisfy the enablement requirement. The facts are that the Office Action of March 3, 2009 rejected claims 1-47 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. (See page 5, sections 8-10 of Office Action of 3-3-09.)

The Action asserted that the Applicants' previous argument that the specification teaches the use of LASERGENE software to assist in determining which amino acid residues can be changed without a loss of biological activity or the ability to form particles is not convincing. However, this assertion is respectfully disagreed with.

The Action asserts that Example 14 and Table 13 are evidence that changes of two or three amino acids (less than 5% substitution) in the HBc SEQ ID NO:1 sequence totally abolish their ability to form particles. This argument is not on point. Applicants are not merely claiming chimeric molecules with 5% substitution, but also that those are chimeric HBc protein molecules in which *one or both cysteine residues at positions 48 and 107 is replaced by another residue*. This recitation has not been taken into account in the Action's arguments. Moreover, the claims also contain another recitation not taken into account, namely that the substitutions be *conservative* substitutions that preserve the structural and functional integrity of the molecule. (See paragraphs [0081] and [0231]-[0234].)

The "Definitions" section of the present application, under the term "corresponds" states that peptide sequences described contain only conservative substitutions along the

polypeptide sequence. (See paragraph [0081].) Furthermore, in paragraph [0231], the specification relates that the contemplated chimers contain conservative substitutions in the amino acid residues that constitute domains I-IV of the HBc sequence. Also, paragraph [0232] states that guidance in determining which amino acid residues can be substituted, inserted or deleted without abolishing biological activity or particles formation can be found using computer programs known in the art such as LASERGENE. Still further, paragraph [0234] states that substitutions are preferably in the non-helical portions of the molecule between residues 2-15 and 24-50 to help assure particle formation, citing Koschel et al., (1999) *J. Virol.*, 73(3): 2153-2160.

Simply put, the above passages illustrate that the specification describes and enables chimeric HBc molecules with conservative amino acid substitutions that retain biological activity and structural integrity. Based upon these passages, it is submitted that one of ordinary skill in the art would be able to make and use such HBc chimers.

In specific detail, the specification points out that the amino acid substitutions are to be up to 5% of the sequence, that the substitutions are to be conservative, that guidance as to proper conservative substitutions can be obtained with

LASERGENE software and the like, and that the region of substitution is in the non-helical portion of the molecule, within residues 2-15 or 24-50, to assure particle formation.

Also, Fig. 1 describes several more examples of conservative substitutions in the various human viral strains and included as SEQ ID NOs:1-4. Examination of those sequences shows seven possible substitutions that can be made in the *ayw* sequence of SEQ ID NO:1 from positions 2-156. Additionally, paragraph [0234] states that a contemplated chimer of 183 HBc residues can contain up to about 36 residues that are different than those of SEQ ID NO:1, and most preferably, about 5 residues are different. Paragraph [0231] states that an illustrative conservative substitution is seen in the replacement of residues at positions 2 and 3, aspartic acid and isoleucine (DI) by glutamic acid and leucine (EL) residues. Further illustrative examples are the replacement of lysine residues at positions 7 and 97 by arginine residues. It is submitted that these examples of illustrative substitutions are more than a sufficient number to constitute enablement.

The Court has held that it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim. *In re*

Angstadt and Griffin, 190 USPQ 214 (CCPA 1976). Therefore, it is respectfully requested that this rejection be withdrawn.

3) A Prima Facie Case of Obviousness Has Not Been Established as to Claims 1-6, 8-14, 16-28, 30-42, and 46

a) In contrast to allegations asserted in the Final Office Action, Claims 1-6, 8-14, 16-28, 30-42, and 46 are not obvious over the teachings of Pumpens in view of Zlotnick and Zheng. The facts are that the Office Action of March 3, 2009 rejected claims 1-6, 8-14, 16-28, 30-42, and 46 under 35 U.S.C. §103, as obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) and Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429). The Action alleged that this rejection is maintained for the reasons of record. (See, page 6, sections 11-16 of Office Action of 3-3-09.)

In the last Response, it was argued that the combination of Zlotnick, Zheng and Pumpens does not teach that the modification of cysteines at positions 48 and 107 of HBc and the addition of a cysteine residue at the C-terminus of the molecules. [Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74); Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) and Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429)] This argument was rejected for reasons of record.

Going back to the November 17, 2006 Office Action, the 103 rejection on page 6, section 19, upon which the current rejection is piggy-backed, the following was alleged: Pumpens teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules of a variety of lengths up to about 380 or 600 amino acid residues in length. Pumpens teaches that both full-length and C-terminal truncated HBc molecules can form particles. Also that HBc and HBc chimers can carry B-cell and T-cell epitopes at the N-terminus, C-terminus or at an internal loop at positions 76-85 (citing Pumpens' Fig. 1 and Tables 1-3). Pumpens also teaches that such chimers can contain two epitopes at both the immunodominant loop and C-terminus (citing Table 2). These chimers contain an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule (citing Fig. 1) that include a peptide-bonded heterologous epitope (citing Table 1) of a heterologous linker residue. Pumpens discloses that HBc chimeras with C-terminal truncations are capable of self-assembly and do not bind nucleic acids (citing page 67, col. 1). Also it was alleged that Pumpens does not explicitly teach replacement of one or both cysteine residues at positions 48 and 107 by another residue and also does not teach that adding a C-terminal cysteine to stabilize the chimeric molecule.

The Action alleged that Zlotnick teaches that residues 150-183 at the C-terminus were required for RNA packaging and that deletion of this region resulted in capsids free of RNA (citing Abstract, p. 9556, p. 9560). Zlotnick is also said to teach that the addition of a single heterologous cys at the C-terminus can stabilize the virus capsid dimers after deletion of the protamine domain 150-183. Zlotnick shows that the Cp*150 capsids, in which three native cys 48, 61 and 107 are replaced by three Ala, and a single heterologous cys is added to position 150 after deletion of its protamine domain 150-183, forms disulfide dimers at pH 7.5 but not pH 9, but not cys-free Cp*149 (citing Fig. 2, right column). Zlotnick has shown that the Cp*150 capsid is more stable than not cys-free Cp*149 and can resist dissociation by 3.5 M urea, suggesting that disulfide bond formation by Cp*150 can promote capsid assembly (Results and Discussion, paragraphs 1 and 2, p. 9558.).

The Action alleged that Zheng teaches the function of native cysteines in formation of HBc particles. Zheng teaches that the intra-chain disulfide bonds are not essential for core particle formation but interchain disulfide bonds are involved in the formation of HBc capsid dimers with the identical residues of another monomer. Zheng teaches that the native Cys107 is buried within the particles structure and is not

involved in HBc capsid formation. The native Cys61 and Cys183 are always involved in interchain disulfide bonds with identical residues of another monomer and the Cys48 is partially involved.

Therefore, the Action alleged that it would have been obvious to make a C-terminal truncated HBc chimer containing one or two epitopes at its N-terminus, C-terminus, or immunodominant loop, in which Cys48 and/or Cys107 are conservatively replaced by another residue and a heterologous Cys is added at the C-terminus.

First, it is agreed that Pumpens does not explicitly teach one or both cysteine residues at positions 48 and 107 by another residue and also does not teach that adding a C-terminal cysteine to stabilize the chimeric molecule.

Second, Pumpens states on page 67, first paragraph, that capsids formed by C-terminally truncated HBc monomers are less stable than are the corresponding full-length protein particles. Pumpens then cites three references to back up that statement (citing References 25, 44, and 45). After reading that statement about unstable C-terminally truncated molecules, one of skill in the art would be disinclined to make such truncated molecules, and thus Pumpens teaches away from that aspect of the present invention.

Additional evidence that Pumpens teaches away from the present invention can be found on page 67, column two of the article, where it is stated that elimination of 4 or 11 amino-terminal residues resulted in the complete disappearance of chimeric protein in *E. coli* cells (citing references 5 and 49). One of skill in the art would be further discouraged from making truncated HBc molecules after reading Pumpens.

Third, the data in Table 1 on page 66 of Pumpens show that 25% of the HBc constructs made were unable to assemble into capsid particles (see hCG, *E. coli*; FMDV VP1, *E. coli*; HBV pre S2, *E. coli*, and HIV1, gp120, *E. coli*) This demonstration of poor capsid-forming ability and/or capsid instability illustrates that many chimeric particles would be poor candidates for vaccines and therefore teaches still further away from the present invention.

It must be noted that the reliance on Fig. 1 of Zlotnick is misplaced. Zlotnick teaches substitution of all of Cys48, Cys61, Cys107, and Arg150. The present invention requires the substitution of only Cys48 and Cys107. Also, the present invention mandates the presence of Cys61. Zlotnick has no teaching of adding a sequence to HBc to make a chimer. There is no suggestion in Zlotnick to make the present chimers as recited in the claims.

There is also a significant problem with Fig. 1 of Zlotnick upon which the Action heavily relied in its arguments. There is no control molecule such as Cp150 in the set of molecules made. For instance, in the Cp149 series of molecules that contains the HBc sequence through residue 149, there is the Cp149 molecule with no amino acid substitutions. There also is the Cp*149 molecule that has 3 cys substitutions. Therefore, one of ordinary skill could compare the effects of the cys substitutions with the properties of the unsubstituted molecule, Cp149. However, in the case of Cp*150, there are 4 amino acid substitutions and no control molecule of 150 amino acids with no amino acid substitutions with which to compare. Therefore, it is impossible to accurately state what the effects of those 4 amino acid substitutions are on the molecule.

An acknowledgement of the importance of molecule length is made by Zlotnick when he states that truncating the protein by two residues renders it incapable of assembly (see page 9556, second col., first paragraph). Therefore, it is necessary to have a control molecule of the same amino acid length, such as Cp150, in order to glean any accurate information about the effects of those 4 amino acid substitutions in the Cp*150 molecule.

One of skill in the art would also recognize that in order to make any conclusions about the effect of a C-terminal cysteine, there would have had to be a second Cp150 control, where all the cysteines remain unchanged and only the Cp150 C-terminal amino acid is changed. With this molecule for comparison, one of skill in the art could accurately determine the changes in stability due to the presence or absence of a C-terminal cysteine. As it stands, there is no comparison to be made, so no reliable conclusions can be drawn.

In this regard and in response to previous arguments made in previous Responses, the Action maintained that this was a peer-reviewed, published journal so the results are not suspect. This belief is completely off-base and irrelevant.

One of skill in the art would not and does not believe anything and everything simply because it has been produced in a peer-reviewed journal. It is common knowledge that one of skill in the art routinely disbelieves and disagrees with evidence presented in a published journal. Still further, some of the most eminent peer-reviewed journals have recently published retractions of previously well heralded articles, such as the stem cell paper from Hwang Woo-suk and co-workers that was retracted from *Science* in 2006.

Next, the Action incorrectly argued that Zlotnick teaches that the addition of a heterologous cysteine residue at the C-terminus "can stabilize virus capsid dimers . . ." (Action of November 17, 2006 at page 7), and that data from studies with Cys-free-Cp*150 and not Cys-free Cp*149 in 3.5 M urea suggest that disulfide bond formation by Cp*150 can promote capsid stability (Action of November 17, 2006; at page 8, citing page 9558, par. 1 and 2). This allegation is not correct.

First, Zlotnick's Figure 1(b) shows that the non-disclosed Cp150 molecules are dimerized via a disulfide bond at position 61. So much for the value of peer review in permitting a comparison with a hypothetical molecule not referred to as such. That error notwithstanding, the figure shows that the dimers are themselves dimerized via the Cys at position 150.

Examining the SDS/PAGE results of Figure 2(a), one sees bands at molecular mass of about 15-20 kDa in lanes 1-3, 5 and 7, with a light shadow in lane 6. That mass is that of a single non-dimerized, truncated Cp molecule. The bands at greater than 31 kDa in lanes 6 and 7 are the dimers. The shadow in lane 7 at a mass 45-66 kDa is a dimer of dimers like that shown in Figure 1(b).

Zlotnick states that purified Cp*149 and Cp*150 assemble into capsids *under the same conditions* as other Cp

constructs. (See page 9558, first par.) Surely one of skill in the art would recognize that if there were some stability enhancement due to the presence of the C-terminal Cys, there would also most likely be some difference in the conditions of particle assembly. There is none and that speaks to teaching no advantage as to having a C-terminal chimer.

Moreover, Zlotnick emphasizes that these capsids were *indistinguishable* by negative staining electron microscopy and sedimentation on sucrose gradients. Again this teaches one of skill in the art that there seems to be no advantage in having a C-terminal cysteine.

In fact, it is equally plausible that the substitution of arginine with another amino acid at the C-terminus led to increased stability of that molecule. It is conceivable that the C-terminal arginine is destabilizing to the molecule. This is especially plausible in the absence of a proper control molecule, as stated above. Cp149 is not a proper control for Cp*150. The length is not the same. As such, it cannot be reasonably concluded by one of skill in the art that the C-terminal cysteine was responsible for the alleged increased stabilization. It must also be noted that Zlotnick was not looking for ways to increase the stability of capsid particles,

and that is probably why he chose not to issue such a conclusion, especially in the absence of proper controls.

Truly, Zlotnick suggests that other forces are at work besides cysteine binding in terms of capsid assembly. He states that binding of Au11 to Cp*150 induces capsid assembly. He suggests that this binding of Au11 may induce small changes in molecular surfaces near the C-terminus that dock together when dimers polymerize and stimulate the assembly process. (See page 9560, col. 2, first paragraph.) Zlotnick states that the data show that Au cannot cross-link subunits nor coordinate C-terminal cysteines, yet the binding of Au11 to Cp*150 induces capsid assembly. Therefore, one of skill in the art would not conclude that C-terminal cysteines are responsible for capsid stabilization, but rather the opposite, that they are not so important.

All in all, Zlotnick does not provide valid support for the premise that C-terminal cysteines enhance stability because Zlotnick's data lacks the proper controls. As a consequence, conclusions gleaned from it are suspect. Furthermore, Zlotnick himself suggests that other factors come into play regarding inducing capsid assembly and stability, such as changes in molecular surfaces.

Moreover, Zlotnick makes no mention of the insertion of foreign epitopes at the N-terminus, C-terminus or at the internal loop of the HBc sequence as is recited in the present claims.

It is more importantly submitted that any argument based on the effect of a C-terminal cysteine is not relevant to the claims such as claim 25 that recites that the formed particles

> are more stable by size exclusion chromatography after storage at 37° C in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107, (Claim 25, last sub-paragraph).

Thus, whether the C-terminal Cys is present or not present is not relevant to these claims because the molecules that are compared in the claims, being "otherwise identical" would both either have or not have that C-terminal Cys. The presence or absence of a C-terminal cysteine is thus not relevant to the patentability of these claims.

It cannot be agreed with that Zheng teaches interchain disulfide bonds are involved in the formation of HBc capsid dimers as alleged in the Action. Zheng states over and over that "disulfide bonds are not essential for core particle

(capsid) formation." (See page 9422, Abstract, lines 13-14). Zlotnick reinforces that position by writing that purified Cp*149 and Cp*150 assemble into capsids *under the same conditions* as other Cp constructs. As another example,

> [t]he fact that all of the proteins [referring to two wild-type and 12 mutants] were obtained as core particles clearly demonstrates that particle formation is not dependent on (1) the arginine-rich carboxyl-terminal domain of 22-kDa HBcAg (2) the binding of nucleic acid or (3) *the formation of disulfide bonds.* (emphasis added, see page 9426, first paragraph).

Moreover, Zheng repeatedly states that "[a]ll of the proteins [referring to two wild-type and 12 mutants] were shown to have very similar physical and immunochemical properties. All assemble into essentially identical core particle structures." (See Abstract, page 9422) Further, Zheng relates "all of the proteins [referring to two wild-type and 12 mutants] must be very similar in each of these properties [referring to size, charge, etc.]. Their similarity is attested to by electron microscopy, circular dichroism, and antigenic activity." (See page 9426, first paragraph.)

Therefore, the relied-on teachings are not properly combinable to arrive at the currently claimed invention. The current claims are not obvious in light of the combination of

the combined teachings of Pumpens, Zlotnick and Zheng, and it is respectfully requested that this rejection be withdrawn.

4) A *Prima Facie* Case of Obviousness Has Not Been Established Against Claims 1-6, 8-14, 16-28, 30-42, and 46

In contrast to allegations asserted in the Office Action, Claims 1-6, 8-14, 16-28, 30-42, and 46 are not obvious over the disclosures of Page and Birkett in view of Zheng. The facts are that the Office Action of March 3, 2009 rejected claims 1-6, 8-14, 16-28, 30-42, and 46 under 35 U.S.C. §103, as allegedly obvious over the combined teachings of Page et al. (WO 01/98333) and Birkett (U.S. Patent Number 6,231,864) in view of Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429). The Action alleged that this rejection is maintained for the reasons of record. (See page 6, sections 11-16 of Office Action of 3-3-09)

Going back to the Office Action of November 17, 2006, the Action alleged that Page teaches the use of HBcΔ (truncated HBc) as a vehicle for the presentation of B-cell and T-cell epitopes and that the retention of a C-terminal cysteine is important for the formation of a stable particle. It was also alleged that the epitopes could be added at either terminus or at the el loop. (See, page 9, section 26 of 11-17-06 Office Action.) It was further alleged that Page does not explicitly teach incorporating a heterologous linker residue for a

conjugated epitope or substitution of cysteines 48 and/or 107. (See, page 9, section 27.)

Next, the Action alleged that Birkett teaches the incorporation of a heterologous linker such as lysine between positions 76-85.

Lastly, the Action reiterated that the relevance of Zheng has been previously set forth and therefore that the current claims were obvious in light of this combination of art.

This rejection is respectfully disagreed with. However, it is agreed that Page does not teach the substitution of cysteines 48 and 107. Moreover, Page does not teach the importance of the retention of cys61 as is present in the claimed chimeric particles. In addition, Page does not teach the inclusion of an epitope at the N-terminus of the molecule. Therefore, the molecules of Page and the currently claimed molecules are very different. As such, because of these significant differences, whatever Page may teach is not relevant to the presently claimed molecules, and cannot overcome the deficiencies or the remaining art.

Birkett does not teach substitution of cysteines 48 and/or 107 with another amino acid. Birkett also does not address that adding a terminal cysteine lends stability to such a molecule.

The deficiencies in the teachings of Zheng have been noted above.

Therefore, as before, when the skilled worker sums the teachings of the relied-on art, he/she does not know what to keep in and what to omit. The signposts are lacking. As a consequence, the present invention as a whole is not and was not *prima facie* obvious based on the combined teachings of this art. It is respectfully requested that this rejection be withdrawn.

5) Claims 1-46 Are Not Obvious under Obviousness-Type Double Patenting

The Action asserted that claims 1-46 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claims 1-78 of 09/930,915; (2) claims 1-53 of 10/787,734; (3) claims 98-109 of 10/805,913; (4) claims 79-115 of 10/806,006; (5) claims 47-85 of 11/508,655; (6) claims 1-22, 25, 26 of 11/507,083.

The Examiner's comments about obviousness-type double patenting are noted. It must be pointed out that patent application No. 10/805,913 has been abandoned; patent application No. 10/806,006 has been abandoned; and application No. 10/787,734 has issued as U.S. Patent Number 7,361,352. In the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of

the allowed claims and those of the patent. It is believed to be premature to deal with a terminal disclaimer at the present time.

6) Claims 1-6, 8-28, and 30-46 Are Not Obvious under Obviousness-Type Double Patenting

The Action asserted that claims 1-6, 8-28, and 30-46 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent Number 6,231,864 in view of Page et al. (WO 01/98333) and Zheng (*J. Biol. Chem.*, 1992, vol. 267, pp9922-9429).

The Examiner's comments about obviousness-type double patenting are noted. As noted before, in the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of the language of the allowed claims and those of the patent. It is believed to be premature to deal with a terminal disclaimer at the present time.

CLAIMS SUPPORT SECTION

Claims 1, 11, 25, and 47 are the only independent claims. The rest of the claims are dependent on these claims. Support for each claim in the specification is detailed below.

Claims

1. A recombinant chimer hepatitis B core (HBc) protein molecule up to about 600 amino acid residues in length that

(a) contains an HBc sequence of at least about 125 of the N-terminal 183 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present; **[See published Application No. US2004/0146524, par. 0088 and par. 0058]**

(b) contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, in the HBc immunodominant loop between residue positions about 76 through about 85 or the C-terminus of the chimer, and wherein **[par. 0036]**

[(i)] (1) zero to all residues in a sequence in said HBc immunodominant loop are present or replaced and said

heterologous amino acid residue sequence comprises one to about 245 amino acid residues that constitute an immunogen or a sequence of 1 to about 40 residues that constitutes an anti-antigen or a chemically-reactive linker residue for a conjugated hapten; or **[par. 0036]**

[(ii)] (2) the sequence of HBc at positions 76 through 85 is present and free from deletions and heterologous residues; or **[par. 0036]**

[(iii)] (3) one or more of residues 76 through 85 is absent or replaced; **[par. 0036]**

(c) contains one or both of

[(i)] (1) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and **[par. 0034]**

[(ii)] (2) one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]; said chimer molecule **[par. 0036]**

(i) having an amino acid sequence in which up to about 5 percent of the amino acids are substituted in the HBc chimer sequence corresponding to SEQ ID NO:1, and **[par. 0036]**

(ii) self-assembling into particles that exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7 after expression. **[par. 0042]**

2. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein the N-terminal sequence includes a heterologous sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4 that includes an immunogenic epitope. **[par. 0036]**

3. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein the sequence of HBc at position about 76 through about 85 is present and free from deletions and heterologous residues. **[par. 0036]**

4. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein zero to all residues in a sequence of HBc positions 76 through 85 are present and peptide-bonded to one to about 245 amino acid

residues that are heterologous to HBc and constitute a heterologous epitope. **[par. 0036]**

5. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein one or more of residues 76 through 85 is absent or replaced. **[par. 0036]**

6. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein the C-terminal sequence contains up to about 100 amino acid residues that include an immunogenic epitope in a sequence heterologous to HBc and bonded to said C-terminal residue of the HBc sequence. **[par. 0036]**

7. (rejected) The recombinant chimer hepatitis B core (HBc) protein molecule according to claim 1 wherein the HBc residue at each of positions 76 and 82 is replaced by a cysteine residue. **[par. 0095]**

8. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 that contains an HBc sequence of at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule. **[par. 0096]**

9. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 that is up to about 380 amino acid residues in length. **[par. 0037]**

10. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 that contains at least about 135 of the N-terminal 163 amino acid residues of HBc. **[par. 0038]**

11. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 380 amino acid residues in length that **[par. 0037]**

(a) contains an HBc sequence of at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present; **[par. 0038], [par. 0058]**

(b) includes one or more of the following:

(i) a peptide-bonded heterologous sequence of up to about 75 residues at one or more of the N-terminus, in

the HBc immunodominant loop and at the C-terminus of the chimer wherein that C-terminal sequence is other than that of HBc from position 163 through the native HBc C-terminus, **[par. 0038]**

(ii) zero to all of the residues of the sequence of position about 76 through about 85 are present or replaced , wherein **[par. 0036]**

(iia) said heterologous sequence of up to about 75 amino acid residues is peptide-bonded to the sequence between about positions 76 through about 85, or **[par. 0090]**

(iib) a sequence of one to about 40 amino acid residues that constitute an anti-antigen is peptide-bonded to the sequence between about positions 76 through about 85, or **[par. 0091]**

(iic) a chemically-reactive linker residue for a conjugated hapten is peptide-bonded to the sequence between about positions 76 through about 85, or **[par. 0091]**

(iid) the sequence of HBc at position about 76 through about 85 is present and free from deletions and heterologous residues, or **[par. 0091]**

(iie) one or more of residues about 76 through about 85 is absent or replaced; **[par. 0092]**

(c) contains one to three cysteine residues present **[par. 0098]**

(i) at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, or **[par. 0098]**

(ii) toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], or at both locations (i) and (ii); **[par. 0098]**

(d) has an amino acid sequence in which up to about 5 percent of the amino acids are substituted in the HBc chimer sequence corresponding to SEQ ID NO:1, and **[par. 0036]**

(e) self-assembles into particles after expression that upon collection, purification and dissolution, exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7. **[par. 0090]**

12. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 11 that contains one to three C-terminal cysteine residue(s). **[par. 0089]**

13. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 11 that contains at least about 135 of the N-terminal 163 amino acid residues of HBc. **[par. 0096]**

14. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 13 that contains an HBc sequence of at least about 135 of the N-terminal 156 amino acid residues of the HBc molecule. **[par. 0096]**

15. (rejected) The recombinant chimer hepatitis B core (HBc) protein molecule according to claim 11 wherein the residue of HBc at each of positions 76 and 82 is replaced by a cysteine residue. **[par. 0095]**

16. (rejected) The recombinant HBc chimer protein molecule according to claim 11 wherein said peptide-bonded sequence of up to about 75 residues is present. **[par. 0093]**

17. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the N-terminus of the chimer. **[par. 0090]**

18. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said peptide-bonded sequence of up to about 75 residues is present bonded in the HBc immunodominant loop of the chimer. **[par. 0093]**

19. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the C-terminus of the chimer. **[par. 0036]**

20. (rejected) The recombinant HBc chimer protein molecule according to claim 16 that contains a second peptide-bonded sequence of up to about 75 residues present bonded to the N-terminus, in the HBc immunodominant loop or to the C-terminus of the chimer at a position different from that to which the first-named sequence of up to about 75 residues was bonded. **[par. 0130]**

21. (rejected) The recombinant HBc chimer protein molecule according to claim 20 wherein said first-named sequence of up to about 75 residues contains a B cell epitope. **[par. 0130]**

22. (rejected) The recombinant HBc chimer protein molecule according to claim 21 wherein said second-named sequence of up to about 75 residues contains a T cell epitope. **[par. 0131]**

23. (rejected) The recombinant HBc chimer protein molecule according to claim 11 wherein both cysteine residues at positions 48 and 107 are replaced by another residue. **[par. 0141]**

24. (rejected) The recombinant HBc chimer protein molecule according to claim 23 wherein the replacement residue for each cysteine is selected from the group consisting of glutamine, asparagine, serine, alanine, threonine and lysine. **[par. 0096]**

25. (rejected) A recombinant hepatitis B virus core (HBc) protein chimer molecule that has a length of about 135 to about 365 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein **[par. 0044]**

Domain I comprises about 72 to about 150 amino acid residues whose sequence includes: **[par. 0045]**

[(i)] (a) at least the sequence of the residues of position 4 through position 75 of HBc, **[par. 0046]**

[(ii)] (b) the substitution of another residue for the cysteine residue at position 48, while maintaining the cysteine at residue position 61, **[par. 0047]**

[(iii)] (c) zero to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, and **[par. 0048]**

[(iv)] (d) an optional immunogenic epitope sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4; **[par. 0049]**

Domain II comprises up to about 60 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which those peptide-bonded amino acid residues comprise **[par. 0108]**

(a) the sequence of 10 residues of HBc positions 76 through 85 present, but interrupted by **[par. 0112]**

[(i)] (1) one to about 50 residues of a heterologous immunogen-containing sequence, or **[par. 0112]**

[(ii)] (2) 1 to about 40 residues of an anti-antigen-containing sequence, or **[par. 0112]**

[(iii)] (3) 1 to about 40 residues of a sequence containing a chemically-reactive linker residue for a conjugated hapten, or **[par. 0112]**

(b) the sequence of HBc positions 76-85 is present with two replacement cysteine residues at HBc positions 76 and 82, and includes an interrupting sequence of **[par. 0112]**

[(i)] (1) up to 50 residues of a heterologous immunogen-containing sequence, or **[par. 0112]**

[(ii)] (2) 1 to about 40 residues of an anti-antigen-containing sequence; or **[par. 0112]**

[(iii)] (3) 1 to about 40 residues of a sequence containing a chemically-reactive linker residue for a conjugated hapten; **[par. 0112]**

Domain III comprises an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II in which another residue is substituted for the cysteine of position 107; **[pars. 0113, 0087]**

Domain IV comprises:

[(i)] (a) five through about thirty residues of an HBc amino acid residue sequence from position 136 through about 165

peptide-bonded to the residue of position 135 of Domain III, **[par. 0115]**

[(ii)] (b) zero to three cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, **[par. 0116]**

[(iii)] (c) zero to about 75 amino acid residues in a sequence other than that present in HBc from position 165 to the C-terminus, and the sequence of the chimer molecule from HBc position 150 through the C-terminus of the chimer molecule contains fewer than about ten arginine or lysine residues or mixtures of both residues; said chimer molecule **[pars. 0117, 0056]**

(i) having an amino acid residue sequence in which up to about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to SEQ ID NO:1, **[par. 0036]**

(ii) having at least one cysteine residue present from the recited zero to three cysteine residues of Domains I and IV, and **[par. 0058]**

(iii) self-assembling into particles on expression by a host cell wherein the particles so formed exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7 and are more stable by size exclusion

chromatography after storage at 37° C in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107. **[par. 0105]**

26. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 25 that contains one to three C-terminal cysteine residue(s). **[par. 0036]**

27. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 25 that contains at least about 135 of the N-terminal 156 amino acid residues of HBc. **[par. 0096]**

28. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 27 that contains an HBc sequence of at least about 135 of the N-terminal 149 amino acid residues of the HBc molecule. **[par. 0038]**

29. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 25 wherein the residue of

HBc at each of positions 76 and 82 is replaced by a cysteine residue. **[par. 0095]**

30. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein a peptide-bonded sequence of up to about 75 residues is present. **[par. 0032]**

31. (rejected) The recombinant HBc chimer protein molecule according to claim 30 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the N-terminus of the chimer. **[par. 0036]**

32. (rejected) The recombinant HBc chimer protein molecule according to claim 30 wherein said peptide-bonded sequence of up to about 75 residues is present bonded in the HBc immunodominant loop of the chimer. **[par. 0036]**

33. (rejected) The recombinant HBc chimer protein molecule according to claim 30 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the C-terminus of the chimer. **[par. 0036]**

34. (rejected) The recombinant HBc chimer protein molecule according to claim 30 that contains a second peptide-bonded sequence of up to about 75 residues present bonded to the N-terminus, in the HBc immunodominant loop or to the C-terminus of the chimer at a position different from that to which the first-named sequence of up to about 75 residues was bonded. **[par. 0130]**

35. (rejected) The recombinant HBc chimer protein molecule according to claim 34 wherein said first-named sequence of up to about 75 residues contains a B cell epitope. **[par. 0130]**

36. (rejected) The recombinant HBc chimer protein molecule according to claim 35 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present. **[par. 0147]**

37. (rejected) The recombinant HBc chimer protein molecule according to claim 36 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope. **[par. 0147]**

38. (rejected) The recombinant HBc chimer protein molecule according to claim 35 wherein said second-named sequence of up to about 75 residues contains a T cell epitope. **[par. 0147]**

39. (rejected) The recombinant HBc chimer protein molecule according to claim 38 wherein said T cell immunogenic epitope is peptide-bonded to the C-terminal HBc amino acid residue. **[par. 0176-0177]**

40. (rejected) The recombinant HBc chimer protein molecule according to claim 39 wherein at least one of said C-terminal cysteine residue(s) is present. **[par. 0176]**

41. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein said chimer contains the uninterrupted HBc amino acid residue sequence of position 4 through at least position 140, plus a cysteine residue at the C-terminus of the HBc chimer protein molecule. **[par. 0227]**

42. (rejected) The recombinant HBc chimer protein molecule according to claim 41 wherein said chimer contains the

uninterrupted HBc amino acid residue sequence of position 4 through position 149. **[par. 0227]**

43. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein said chimer contains a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop. **[par. 0036]**

44. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present. **[par. 0147]**

45. (rejected) The recombinant HBc chimer protein molecule according to claim 44 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope. **[par. 0227]**

46. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein the residue substituted

for each cysteine at positions 48 and 107 is individually selected from the group consisting of glutamine, asparagine, serine, alanine, threonine and lysine. **[par. 0096]**

47. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 600 amino acid residues in length that

(a) contains an HBc sequence of at least about 125 of the N-terminal 183 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present; **[pars. 0088, 0058]**

(b) contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, in the HBc immunodominant loop between residue positions about 76 through about 85, and the HBc residue at each of positions 76 and 82 is replaced by a cysteine residue, or the C-terminus of the chimer, and wherein **[pars. 0036, 0095]**

[(i)] (1) zero to all residues in a sequence in said HBc immunodominant loop other than at positions 76 and 82 are present or replaced and said heterologous amino acid

residue sequence comprises one to about 245 amino acid residues that constitute an immunogen or a sequence of 1 to about 40 residues that constitutes an anti-antigen or a chemically-reactive linker residue for a conjugated hapten; or **[pars. 0036, 0112]**

[(ii)] (2) one or more of residues 76 through 85 other than the cysteines at positions 76 and 82 is absent or replaced; **[par. 01112]**

(c) contains one or both of

[(i)] (1) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and **[par. 0104]**

[(ii)] (2) one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]; said chimer molecule **[par. 0116]**

(i) having an amino acid sequence in which up to about 5 percent of the amino acids are

substituted in the HBc chimer sequence corresponding to SEQ ID NO:1, and **[par. 0233]**

(ii) self-assembling into particles that exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7 after expression. **[par. 0140]**

CLAIMS APPENDIX

1. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 600 amino acid residues in length that

(a) contains an HBc sequence of at least about 125 of the N-terminal 183 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present;

(b) contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, in the HBc immunodominant loop between residue positions about 76 through about 85 or the C-terminus of the chimer, and wherein

[(i)] (1) zero to all residues in a sequence in said HBc immunodominant loop are present or replaced and said heterologous amino acid residue sequence comprises one to about 245 amino acid residues that constitute an immunogen or a sequence of 1 to about 40 residues that constitutes an anti-antigen or a chemically-reactive linker residue for a conjugated hapten; or

[(ii)] (2) the sequence of HBc at positions 76 through 85 is present and free from deletions and heterologous residues; or

[(iii)] (3) one or more of residues 76 through 85 is absent or replaced;

(c) contains one or both of

[(i)] (1) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and

[(ii)] (2) one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]; said chimer molecule

(i) having an amino acid sequence in which up to about 5 percent of the amino acids are substituted in the HBc chimer sequence corresponding to SEQ ID NO:1, and

(ii) self-assembling into particles that exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7 after expression.

2. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein the N-terminal sequence includes a heterologous sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4 that includes an immunogenic epitope.

3. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein the sequence of HBc at position about 76 through about 85 is present and free from deletions and heterologous residues.

4. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein zero to all residues in a sequence of HBc positions 76 through 85 are present and peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope.

5. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein one or more of residues 76 through 85 is absent or replaced.

6. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 wherein the C-terminal sequence contains up to about 100 amino acid residues that include an immunogenic epitope in a sequence heterologous to HBc and bonded to said C-terminal residue of the HBc sequence.

7. (rejected) The recombinant chimer hepatitis B core (HBc) protein molecule according to claim 1 wherein the HBc residue at each of positions 76 and 82 is replaced by a cysteine residue.

8. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 that contains an HBc sequence of at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule.

9. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 that is up to about 380 amino acid residues in length.

10. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 1 that contains at least about 135 of the N-terminal 163 amino acid residues of HBc.

11. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 380 amino acid residues in length that

(a) contains an HBc sequence of at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present;

(b) includes one or more of the following:

(i) a peptide-bonded heterologous sequence of up to about 75 residues at one or more of the N-terminus, in the HBc immunodominant loop and at the C-terminus of the chimer wherein that C-terminal sequence is other than that of HBc from position 163 through the native HBc C-terminus,

(ii) zero to all of the residues of the sequence of position about 76 through about 85 are present or replaced , wherein

(iia) said heterologous sequence of up to about 75 amino acid residues is peptide-bonded to the sequence between about positions 76 through about 85, or

(iib) a sequence of one to about 40 amino acid residues that constitute an anti-antigen is peptide-bonded to the sequence between about positions 76 through about 85, or

(iic) a chemically-reactive linker residue for a conjugated hapten is peptide-bonded to the sequence between about positions 76 through about 85, or

(iid) the sequence of HBc at position about 76 through about 85 is present and free from deletions and heterologous residues, or

(iie) one or more of residues about 76 through about 85 is absent or replaced;

(c) contains one to three cysteine residues present

(i) at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, or

(ii) toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], or at both locations (i) and (ii);

(d) has an amino acid sequence in which up to about 5 percent of the amino acids are substituted in the HBc chimer sequence corresponding to SEQ ID NO:1, and

(e) self-assembles into particles after expression that upon collection, purification and dissolution, exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7.

12. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 11 that contains one to three C-terminal cysteine residue(s).

13. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 11 that contains at least about 135 of the N-terminal 163 amino acid residues of HBc.

14. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 13 that contains an HBc sequence of at least about 135 of the N-terminal 156 amino acid residues of the HBc molecule.

15. (rejected) The recombinant chimer hepatitis B core (HBc) protein molecule according to claim 11 wherein the residue

of HBc at each of positions 76 and 82 is replaced by a cysteine residue.

16. (rejected) The recombinant HBc chimer protein molecule according to claim 11 wherein said peptide-bonded sequence of up to about 75 residues is present.

17. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the N-terminus of the chimer.

18. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said peptide-bonded sequence of up to about 75 residues is present bonded in the HBc immunodominant loop of the chimer.

19. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the C-terminus of the chimer.

20. (rejected) The recombinant HBc chimer protein molecule according to claim 16 that contains a second peptide-bonded sequence of up to about 75 residues present bonded to the N-terminus, in the HBc immunodominant loop or to the C-terminus of the chimer at a position different from that to which the first-named sequence of up to about 75 residues was bonded.

21. (rejected) The recombinant HBc chimer protein molecule according to claim 20 wherein said first-named sequence of up to about 75 residues contains a B cell epitope.

22. (rejected) The recombinant HBc chimer protein molecule according to claim 21 wherein said second-named sequence of up to about 75 residues contains a T cell epitope.

23. (rejected) The recombinant HBc chimer protein molecule according to claim 11 wherein both cysteine residues at positions 48 and 107 are replaced by another residue.

24. (rejected) The recombinant HBc chimer protein molecule according to claim 23 wherein the replacement residue for each cysteine is selected from the group consisting of glutamine, asparagine, serine, alanine, threonine and lysine.

25. (rejected) A recombinant hepatitis B virus core (HBc) protein chimer molecule that has a length of about 135 to about 365 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

Domain I comprises about 72 to about 150 amino acid residues whose sequence includes:

[(i)] (a) at least the sequence of the residues of position 4 through position 75 of HBc,

[(ii)] (b) the substitution of another residue for the cysteine residue at position 48, while maintaining the cysteine at residue position 61,

[(iii)] (c) zero to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, and

[(iv)] (d) an optional immunogenic epitope sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4;

Domain II comprises up to about 60 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which those peptide-bonded amino acid residues comprise

(a) the sequence of 10 residues of HBc positions 76 through 85 present, but interrupted by

[(i)] (1) one to about 50 residues of a heterologous immunogen-containing sequence, or

[(ii)] (2) 1 to about 40 residues of an anti-antigen-containing sequence, or

[(iii)] (3) 1 to about 40 residues of a sequence containing a chemically-reactive linker residue for a conjugated hapten, or

(b) the sequence of HBc positions 76-85 is present with two replacement cysteine residues at HBc positions 76 and 82, and includes an interrupting sequence of

[(i)] (1) up to 50 residues of a heterologous immunogen-containing sequence, or

[(ii)] (2) 1 to about 40 residues of an anti-antigen-containing sequence; or

[(iii)] (3) 1 to about 40 residues of a sequence containing a chemically-reactive linker residue for a conjugated hapten;

Domain III comprises an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II in which another residue is substituted for the cysteine of position 107;

Domain IV comprises:

[(i)] (a) five through about thirty residues of an HBc amino acid residue sequence from position 136 through about 165 peptide-bonded to the residue of position 135 of Domain III,

[(ii)] (b) zero to three cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule,

[(iii)] (c) zero to about 75 amino acid residues in a sequence other than that present in HBc from position 165 to the C-terminus, and the sequence of the chimer molecule from HBc position 150 through the C-terminus of the chimer molecule contains fewer than about ten arginine or lysine residues or mixtures of both residues; said chimer molecule

(i) having an amino acid residue sequence in which up to about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to SEQ ID NO:1,

(ii) having at least one cysteine residue present from the recited zero to three cysteine residues of Domains I and IV, and

(iii) self-assembling into particles on expression by a host cell wherein the particles so formed exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7 and are more stable by size exclusion chromatography after storage at 37° C in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107.

26. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 25 that contains one to three C-terminal cysteine residue(s).

27. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 25 that contains at least about 135 of the N-terminal 156 amino acid residues of HBc.

28. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 27 that contains an HBc

sequence of at least about 135 of the N-terminal 149 amino acid residues of the HBc molecule.

29. (rejected) The recombinant chimer hepatitis B core protein molecule according to claim 25 wherein the residue of HBc at each of positions 76 and 82 is replaced by a cysteine residue.

30. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein a peptide-bonded sequence of up to about 75 residues is present.

31. (rejected) The recombinant HBc chimer protein molecule according to claim 30 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the N-terminus of the chimer.

32. (rejected) The recombinant HBc chimer protein molecule according to claim 30 wherein said peptide-bonded sequence of up to about 75 residues is present bonded in the HBc immunodominant loop of the chimer.

33. (rejected) The recombinant HBc chimer protein molecule according to claim 30 wherein said peptide-bonded sequence of up to about 75 residues is present bonded at the C-terminus of the chimer.

34. (rejected) The recombinant HBc chimer protein molecule according to claim 30 that contains a second peptide-bonded sequence of up to about 75 residues present bonded to the N-terminus, in the HBc immunodominant loop or to the C-terminus of the chimer at a position different from that to which the first-named sequence of up to about 75 residues was bonded.

35. (rejected) The recombinant HBc chimer protein molecule according to claim 34 wherein said first-named sequence of up to about 75 residues contains a B cell epitope.

36. (rejected) The recombinant HBc chimer protein molecule according to claim 35 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

37. (rejected) The recombinant HBc chimer protein molecule according to claim 36 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

38. (rejected) The recombinant HBc chimer protein molecule according to claim 35 wherein said second-named sequence of up to about 75 residues contains a T cell epitope.

39. (rejected) The recombinant HBc chimer protein molecule according to claim 38 wherein said T cell immunogenic epitope is peptide-bonded to the C-terminal HBc amino acid residue.

40. (rejected) The recombinant HBc chimer protein molecule according to claim 39 wherein at least one of said C-terminal cysteine residue(s) is present.

41. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein said chimer contains the uninterrupted HBc amino acid residue sequence of position 4 through at least position 140, plus a cysteine residue at the C-terminus of the HBc chimer protein molecule.

42. (rejected) The recombinant HBc chimer protein molecule according to claim 41 wherein said chimer contains the uninterrupted HBc amino acid residue sequence of position 4 through position 149.

43. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein said chimer contains a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop.

44. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present.

45. (rejected) The recombinant HBc chimer protein molecule according to claim 44 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope.

46. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein the residue substituted for each cysteine at positions 48 and 107 is individually selected from the group consisting of glutamine, asparagine, serine, alanine, threonine and lysine.

47. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 600 amino acid residues in length that

(a) contains an HBc sequence of at least about 125 of the N-terminal 183 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present;

(b) contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, in the HBc immunodominant loop between residue positions about 76 through about 85, and the HBc residue at each of positions 76 and 82 is replaced by a cysteine residue, or the C-terminus of the chimer, and wherein

[(i)] (1) zero to all residues in a sequence in said HBc immunodominant loop other than at position s 76 and

82 are present or replaced and said heterologous amino acid residue sequence comprises one to about 245 amino acid residues that constitute an immunogen or a sequence of 1 to about 40 residues that constitutes an anti-antigen or a chemically-reactive linker residue for a conjugated hapten; or

[(ii)] (2) one or more of residues 76 through 85 other than the cysteines at positions 76 and 82 is absent or replaced;

(c) contains one or both of

[(i)] (1) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and

[(ii)] (2) one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]; said chimer molecule

(i) having an amino acid sequence in which up to about 5 percent of the amino acids are substituted in the HBc chimer sequence corresponding to SEQ ID NO:1, and

(ii) self-assembling into particles that exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7 after expression.

EVIDENCE APPENDIX

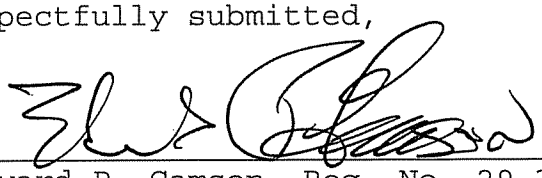
None

RELATED PROCEEDING APPENDIX

None

Favorable consideration of this Appeal and allowance on the captioned application are respectfully requested.

Respectfully submitted,

By 
Edward P. Gamson, Reg. No. 29,381

HUSCH BLACKWELL SANDERS
WELSH AND KATZ LLP
120 South Riverside Plaza, Suite 2200
Chicago, Illinois 60606
Tel.:(312)655-1500
Fax(312)655-1501
Email:edward.gamson@huschblackwell.com

Counsel for Appellants

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